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Modelling Cancer Dynamics in HIV-1 Infected Individuals*

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Abstract: Cancer remains a significant burden for HIV-infected individuals. In this paper, an ODE model and an DDE model about HIV-1 dynamics incorporating the AIDS-related cancer cells in *vitro* a studied. For each model, we discuss the existence, the stability properties and the biological meanings of these steady states. Also we find conditions for Hopf bifurcation of the positive steady state, leading to periodic solutions, sequences of period doubling bifurcations and appearance of chaos. Further, chaos and periodic behavior alternate.

Keywords: HIV; cancer; dynamic model; Hopf bifurcation; chaos

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1 Introduction

Cancer remains a significant burden for HIV-1 infected individuals. Most of these are virus-associated cancers. How can the combination of immunosuppression and activation of inflammation promote cancer development? Our purpose in this paper is to try to give a glancing analysis using two simple dynamical models.

According to the literature[1], the cell-to-cell mechanism of HIV-1 transfer has been estimated to be much more important than infection by free virus particles in lymph tissues, where 98% of the CD4+ T cells in vivo are found. Therefore, an ODE model concerning the cell-to-cell spread of HIV-1 is relevant.

There is a lag between viral infection and viral production: for a normal activated infected CD4+ T cells, it is estimated that the first viral release occurs about 24 hours after the initial infection. While for some quiescent infected lymphocyte cells, the "incubation" phase can last about 60 days[2]. So the second aim of the present paper is to focus the attention on the "incubation" function during the HIV-1 infection and cancer developing.

The basic starting point of this model has three parts. First, the cancer is a single clone mechanism. Second, the cancer cells have some special genes and so they proliferate in a special way which is different from normal cells. Third, considering the key position of CD4+ lymphocyte, we use them to represent the immune system in our model.

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2 The ODE model

We use $C(t)$, $T(t)$ and $I(t)$ to represent the concentrations of cancer cells, healthy cells and infected cells respectively. We develop an ODE model as follows

$$\begin{cases} \dfrac{\mathrm{d}C}{\mathrm{d}t} = C(t)\Big[r_1\Big(1-\frac{C(t)+T(t)+I(t)}{m}\Big) - k_1T(t)\Big], \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = T(t)\Big[r_2\Big(1-\frac{C(t)+T(t)+I(t)}{m}\Big) - pk_1C(t) - k_2I(t)\Big], \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = I(t)\big(k_2T(t)-\mu_I\big). \end{cases} \tag{1}$$

We use parameter r_1 to represent its uncontrolled proliferation rate, k_1 as the immune system's killing rate of cancer cells; m as the effective carrying capacity of the system; r_2 as the intrinsic growth rate of healthy cells and p as the losing rate of the immune cells because of its killing the cancer cells. k_2 is the infection rate coefficient that accounts for the overall effects of HIV-1 reproduction. μ_I represents the whole immune system's killing effect on the infected cells. All the parameter values above are non-negative. We assume initial conditions of $C(0)=C_0,\ T(0)=T_0,\ I(0)=I_0$.

The possible steady states of system (1) are as follows: the trivial steady state, $E_0=(0,0,0)$; the cancer steady state, $E_1=(m,0,0)$; the healthy steady state, $E_2=(0,m,0)$; the cancer-healthy steady state

$$E_3=(\bar{C},\bar{T},0)=\Big(\frac{mr_2}{r_2+p(r_1+mk_1)},\ \frac{mr_1p}{r_2+p(r_1+mk_1)},\ 0\Big);$$

the HIV-healthy steady state

$$E_4=(0,\hat{T},\hat{I})=\Big(0,\ \frac{\mu_I}{k_2},\ \frac{r_2(mk_2-\mu_I)}{k_2(mk_2+r_2)}\Big);$$

and the cancer-HIV-healthy steady state, $E^*=(C^*,T^*,I^*)$, in which

$$C^*=\frac{mr_1k_2^2-(r_1k_2+k_1r_2+mk_1k_2)\mu_I}{r_1k_2(k_2-pk_1)},\quad T^*=\frac{\mu_I}{k_2},$$
$$I^*=\frac{k_1[pmr_1k_2-(r_2+pr_1+pmk_1)\mu_I]}{r_1k_2(pk_1-k_2)}.$$

About the existence and stability of these steady states we have the following results.

Theorem 1 Let

$$R_0=\frac{mk_2}{\mu_I},\quad R_1=\frac{r_1}{k_1}\cdot\frac{k_2(R_0-1)}{mk_2+r_2},\quad R_2=\frac{pr_1(R_0-1)}{r_2+mpk_1}. \tag{2}$$

1) E_0 and E_3 always exist and are unstable; E_1 always exists and is locally stable.

2) When $R_0<1$, E_2 is locally stable, E_4 and E^* do not exist.

3) When $R_0>1$, E_2 is unstable and E_4 exists. When $R_1<1$, E_4 is locally stable; E^* does not exist or if it exists is unstable. When $R_1>1$, E_4 is unstable. When $R_2<1$, E^* exists; otherwise, E^* does not exist.

Theorem 2 1) When $a_1a_2 - a_3 > 0$ holds, here

$$a_1 = \frac{r_1}{m}C^* + \frac{r_2}{m}T^*; \quad a_3 = (k_2 - pk_1)\frac{r_1k_2}{m}C^*T^*I^*,$$

$$a_2 = k_2\Big(\frac{r_2}{m} + k_2\Big)T^*I^* - k_1\Big(\frac{r_1}{m}p + \frac{r_2}{m} + pk_1\Big)C^*T^*,$$

then the infected steady state E^* of system (1) is locally stable.

2) Otherwise, choose parameter r_1 as the crucial parameter. Then a Hopf bifurcation will occur when r_1 passes through the critical value r_1^c, where r_1^c satisfies: a pair of purely imaginary roots exists for the characteristic equation of E^* when $r_1 = r_1^c$; and the transversality condition $\frac{\mathrm{d}}{\mathrm{d}r_1}\mathrm{Re}\lambda_{2,3}|_{r_1=r_1^c} \neq 0$ holds.

We omit the proof here. In biology, when the uncontrolled proliferate rate of the cancer cells r_1 is small, the cancer situation can not be built and only HIV can survive in the individual. Otherwise, the cancer structure will develop soon, possible denoting the AIDS phase in the infected individual.

3 The DDE model

According to the immune response caused by HIV-1 in tissue culture, we employ a fixed delay τ[3]. We propose a DDE model as follows

$$\begin{cases} \dfrac{\mathrm{d}C(t)}{\mathrm{d}t} = C(t)\Big[r_1\Big(1 - \frac{C(t)+T(t)+I(t)}{m}\Big) - k_1T(t)\Big], \\ \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = T(t)\Big[r_2\Big(1 - \frac{C(t)+T(t)+I(t)}{m}\Big) - pk_1C(t) - k_2I(t)\Big], \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = k_2T(t-\tau)I(t-\tau) - \mu_I I(t). \end{cases} \tag{3}$$

We assume constant initial conditions: $C(\theta) = C_0$, $T(\theta) = T_0$, $I(\theta) = I_0$, for any $\theta \in [-\tau, 0]$.

The existence of steady states of system (3) is the same as that for system (3). The stabilities of these steady states will be shown as follows.

Theorem 3 Let R_0, R_1 and R_2 as that in equations (2). Then for the delay system (3), we have E_0 and E_3 is unstable for all $\tau \geq 0$; E_1 is absolutely stable for all $\tau \geq 0$.

When $R_0 < 1$, E_2 is absolutely stable; otherwise, E_2 is unstable for all $\tau \geq 0$ and E_4 exists.

(a) When $R_1 < 1$

(i) If $3\mu_I > mk_2$ holds, then E_4 of system (3) is asymptotically stable for all $\tau \geq 0$;

(ii) If $3\mu_I < mk_2$ holds, then E_4 is asymptotically stable for $\tau < \hat{\tau}_0$, and unstable when $\tau > \hat{\tau}_0$, where

$$\hat{\tau}_0 = \frac{1}{\hat{\omega}_0}\arccos\Big(\frac{(A_4 - A_1A_3)\hat{\omega}_0^2 - A_2A_4}{A_3^2\hat{\omega}_0^2 + A_4^2}\Big).$$

When $\tau = \hat{\tau}_0$, a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from E_4 as τ passes through the critical value $\hat{\tau}_0$.

(b) When $R_1 > 1$, E_4 is unstable for all $\tau \geq 0$. When $R_2 < 1$, E^* exists; suppose $a_1a_2 - a_3 > 0$ holds, then the infected stable state E^* of system (3) is asymptotically stable

when $\tau < \tau_0$, and unstable when $\tau > \tau_0$, where

$$\tau_0 = \frac{1}{\omega_0} \cdot \arccos\left(\frac{b_5\omega_0^4 + [b_1(b_6 - b_4\omega_0^2) - b_2b_5]\omega_0^2 - b_3(b_6 - b_4\omega_0^2)}{(b_6 - b_4\omega_0^2)^2 + b_5^2\omega_0^2} \right).$$

When $\tau = \tau_0$, a Hopf bifurcation occurs; that is, a family of periodic solutions bifurcates from E^* as τ passes through the critical value τ_0.

4 Numerical simulation and discussion

We mainly discuss the mathematical behavior with changing r_1 and k_1. We choose other parameter values as $r_2 = 0.03$, $k_2 = 5\mathrm{e}^{-4}$, $m = 1500$, $\mu_I = 0.3$, $p = 0.1$, then we can obtain the Hopf bifurcations regions for system (1) and (3) shown in Figure 1 (the above two figures). Simulations for system (1) show that, the orbitally asymptotically stable periodic solution and chaos appear alternately with r_1 increasing (the bottom two figures).

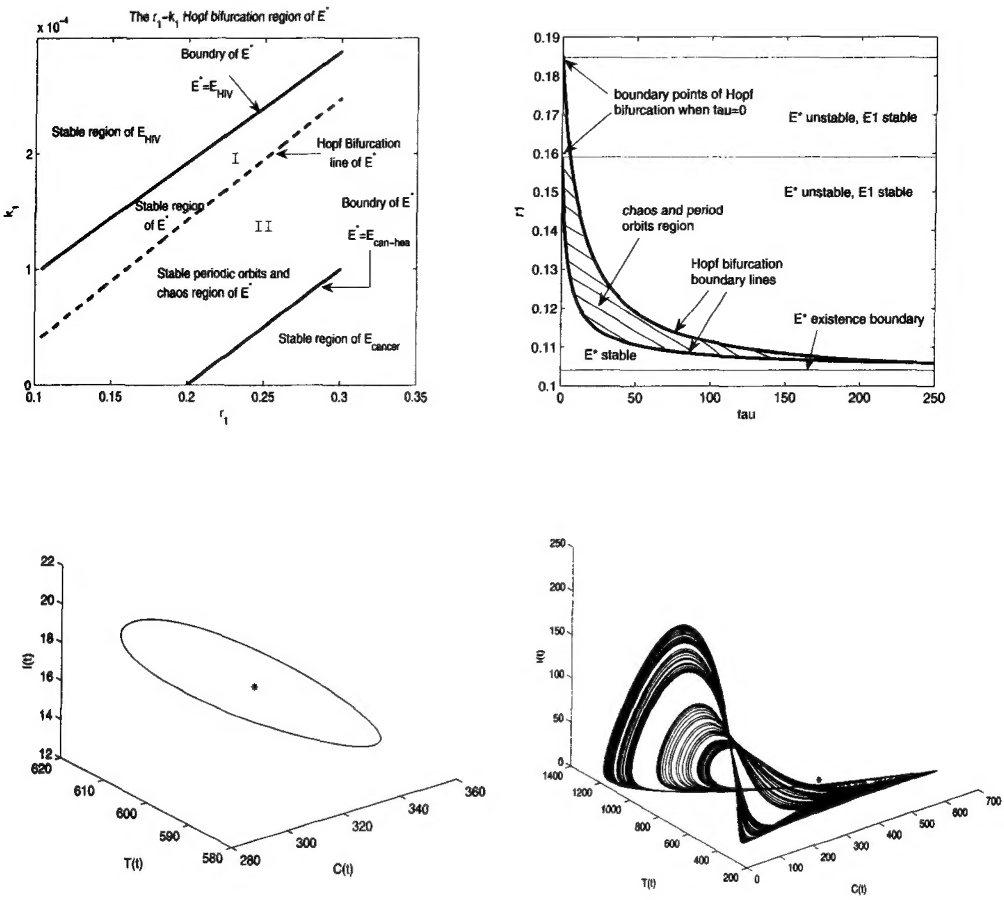

Figure 1: The Hopf bifurcation regions of the ODE model and the DDE model, respectively (the above two figures). Period 1 orbit and chaos appear for $r_1 = r_1^c + 8 \times 10^{-5}$ and $r_1 = r_1^c + 0.0235$ respectively for the ODE model (the botton two figures).

Considering the HIV-1 infection in *vivo*, i.e., considering HIV virus inside the model, we still can find similar results as the two models before. In fact the existence of oscillations and chaos in a biological model is not novel. This phenomenon has been found in clinics[4]. Also, the research on the throb of the human heart and the galvanic activity of the human brain found chaos phenomena[4].

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HIV相关癌症的动力学模型研究

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摘　要: 本文通过建立两个动力学模型，研究了HIV感染者中癌症的高发现象。我们分别研究了其平衡态的存在性及稳定性。对正平衡态还发现了Hopf分支的存在，并发现随着分支参数的变化，系统出现了周期解与混沌交替出现的现象。

关键词: HIV；癌症；动力学模型；Hopf分支；混沌